REMARKS

Applicants have hereinabove amended the title of the subject application to reflect the subject matter of the now pending claims. Applicants maintain that the amendments are supported by the specification as originally filed and thus do not raise any issue of new matter.

Claims 7-9 and 13-25 were pending in the subject application. By this Amendment, applicants have amended claims 7 and 20 to more clearly indicate that the fusion specifically being inhibited is that between a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1 and the envelope of a macrophage-tropic primary HIV-1 isolate. Applicants note that the amendments are fully supported in the specification at, *inter alia*, page 1, line 18 to page 4, line 18; page 5, line 22 to page 6, line 22; page 10, line 3 to page 11, line 26; page 51, line 31 to page 52, line 9; and pages 60-64. Thus, applicants maintain that these amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 7-9 and 13-25, as amended, will be pending and under examination.

Applicants thank the Examiner for the courtesy extended during the telephone interviews with Ashton Delauney, Esq. of the undersigned's office on January 9, and January 24, 2006, and for reviewing a proposed set of amended claims which was forwarded to the Examiner by facsimile on January 18, 2006. These amended claims, which the Examiner informally stated during the January 24, 2006 telephone interview are allowable, are presented hereinabove.

The Invention

The invention claimed in the subject application provides a method of specifically inhibiting fusion of a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1 to an envelope of a macrophage-tropic primary isolate of HIV-1. This method comprises contacting the CD4+ cell with an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, wherein the agent inhibits fusion of the CD4+ cell to the envelope of the macrophage-tropic primary isolate of HIV-1. In embodiments of this invention, the agent may be a protein moiety or a non-protein moiety. Examples of protein moieties include antibodies, such as monoclonal antibodies, and β-chemokines.

Rejections under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 7-9 and 13-25 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen,* 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981); *In re Wertheim,* 541 F.2d 257, 191 U.S.P.Q. 90 (C.C. P.A. 1976)). The Examiner stated that the claims are directed toward methods of inhibiting macrophage-tropic HIV-1 fusion to a $CD4^+$ cell target through the administration of an "agent" that inhibits HIV-1 macrophage-tropic fusion events without inhibiting HIV-1 T-cell tropic fusion events. The Examiner further stated that although the claims have been amended to incorporate additional limitations pertaining to the

nature of the inhibitor (e.g., protein, antibody, chemokine), they still fail to provide sufficient structural and functional limitations. The Examiner also stated that the claims still encompass a large genus of poorly defined chemical compounds which could include, *inter alia*, antibodies, organic compounds, small molecular weight polypeptides, peptidomimetics, and retroinverso peptides.

The Examiner stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (citing, e.g., *Vas-Cath, Inc., v. Mahurkar,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116). The Examiner contended that the issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of "agents" that display preferential inhibitory activities toward NSI-Env-mediated events but not SI-Env-mediated events.

The Examiner stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations, using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)). The Examiner further stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed. The Examiner also stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The Examiner noted that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical

properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

In response, applicants respectfully traverse this "written description" rejection for the reasons set forth below.

With reference to the Examiner's statements that an applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, including (1) binding specificity, (2) functional characteristics alone or coupled with a known or disclosed correlation between function and structure, and (3) the method of making the claimed invention, applicants note that the specification provides disclosures about the "agent" that satisfies each of these identifying characteristics. (Applicants remind the Examiner that the claims are not directed to an agent *per se* but rather to a method of inhibiting HIV-1 fusion. However, applicants herein address the sufficiency of the written description of the "agent" since this is the focus of the instant ground of rejection.) In this regard, applicants assert that the binding specificity of the agent and its preferential inhibitory activities, i.e., its capability, as recited in the pending claims, to inhibit fusion of HIV-1 to one type of cell but not to another, are identifying characteristics of the agent. Applicants note that independent claims 7 and 20, as amended hereinabove, mechanistically define the fusion reaction which is being inhibited. Applicants further assert that the capability of the agent to bind to the target cell is a function of the agent. Moreover, there is clearly a correlation between the function of, and the preferential inhibition exhibited by, the agent. In addition, applicants note that the specification discloses a method (the RET assay) for identifying agents with the properties specified in the claims.

Accordingly, based on the disclosures of these relevant identifying characteristics, applicants maintain that the written description is adequate to show that applicants were in possession of the claimed invention. Applicants further note that, as discussed below, the specification provides working examples of agents which satisfy the requirements recited in the pending claims, namely monoclonal antibodies and β-chemokines.

Applicants refer to the Examiner's statement that the level of skill and knowledge in the art is also a factor to be considered in assessing the sufficiency of the written description. In this regard, applicants note that the level of skill in the biotechnology arts is very high. See, for example, *Enzo Biochem, Inc. v. Calgene, Inc.* 188 F.3d 1362, (Fed. Cir. 1999):

> [T]he district court determined that a person of ordinary skill in the art would be 'a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience,' *see Enzo*, 14 F.Supp.2d at 567, and we discern no clear error in this determination.

Applicants maintain that in an art characterized by high skill, the level of disclosure required to satisfy the written description requirement is less that would be required if the level of skill in the art was low. In support of this position, applicants respectfully direct the Examiner's attention to M.P.E.P. §2163.IIA.2. which states that "[g]enerally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement." Applicants assert that in the instant case, the high level of skill in the art is a favorable factor in assessing the sufficiency of the written description, and maintain that the claimed invention is adequately described in the specification.

The Examiner also stated that rational drug design is facilitated

by knowledge of those regions that are critical for envelope interactions. The Examiner asserted that in the absence of such information, the skilled artisan is essentially being asked to guess as to which agents or compounds might function in the desired manner.

In response, applicants reiterate that, as noted in their January 18, 2005 Amendment, "rational drug design" is not the norm in the pharmaceutical industry. Instead, it remains true that new candidate drugs are normally identified by the screening of large numbers of compounds. Indeed, it was only as recently as the early 1990's that Agouron Pharmaceuticals, Inc. (now part of Pfizer, Inc.) successfully demonstrated the feasibility of rational drug design, i.e., using computerized models of protein molecules to systematically synthesize drugs based on those molecular structures. Applicants maintain that rational drug design is in its infancy and is today still the exception in the pharmaceutical industry. Accordingly, applicants respectfully submit that a rejection predicated on the ground that the specification does not facilitate rational drug design is without merit and should be withdrawn.

The Examiner further stated that the disclosure also fails to provide any guidance pertaining to the structure of any given "agent". The Examiner asserted that the specification provides a small number of β-chemokines that may inhibit NSI-Env-mediated events in a cell-dependent manner but that, however, no other agents or molecules meeting the requirements are disclosed. The Examiner also stated that the lack of a structural/functional correlation fails to lead the skilled artisan to any particular compound. The Examiner asserted that, accordingly, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing.

Applicants respectfully disagree with the Examiner's position. Applicants maintain that information on the structure of any given agent is not required because the nature of an agent which satisfies the requirements of the claims is result-determined. That is, suitable agents are identified on the basis of results of the RET screening assay. Applicants note that the specification discloses a routine, reproducible RET assay for identifying an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, as recited in the pending claims.

Applicants also respectfully point out that the Examiner's statement that the specification provides a small number of β-chemokines that may inhibit NSI-Env-mediated events in a cell-dependent manner but does not disclose other agents meeting the claim requirements is clearly erroneous. In this regard, applicants emphasize that the specification provides data which demonstrate that each of monoclonal antibodies PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see page 60, lines 13-16 and Table 3), but does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell (see Table 3). Applicants note that these are precisely the properties of the agent recited in the pending claims. The data on this preferential antibody binding are additional to the data provided in the specification demonstrating that β-chemokines inhibit fusion of HeLa-env_{JR-FL} to a PM1 cell, but not to inhibit fusion of HeLa-env_{LAI} to a variety of CD4+ cells (see Table 4 on page 63; HeLa-CD4+ cells not specifically tested).

The Examiner noted applicants' traversal of the written description rejections (in their January 18, 2005 Amendment) and their submission that the disclosure provides sufficient written support for the claimed invention. However, the Examiner stated

that this argument is not persuasive for the reasons set forth previously. The Examiner further stated that, moreover, applicants' response fails to provide any objective scientific data addressing the aforementioned caveats. The Examiner queried, for instance, what structural and functional constraints govern the selection of any given agent.

The Examiner contended that the molecular determinants modulating HIV-1 envelope fusion are complex (citing O'Brien *et al.*, 1990). The Examiner also stated that the description provides a generic screening assay for identifying putative macrophage-tropic-specific or T cell-tropic-specific inhibitors, but asserted that this screening assay fails to provide any guidance pertaining to the structure of those compounds that can reasonably be expected to inhibit viral cell fusion. The Examiner also asserted that the skilled artisan cannot reasonably predict the structure of any given inhibitor, and that the disclosure fails to provide sufficient guidance pertaining to this point. According to the Examiner, while the disclosure describes the isolation of four MAbs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T cell-tropic isolates. The Examiner noted that the disclosure clearly states (citing page 60, first paragraph) that "[t]he culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 inhibited fusion between HeLa-env_{JR-FL} and PM1 cells in the RET assay, and also inhibited fusion between HeLa-env_{LAI} cells and certain CD4+ target cells (Table 3)." The Examiner asserted that the disclosure thus fails to identify any suitable agents with the desired properties. The Examiner further asserted that upon perusal of the disclosure, the skilled artisan would reasonably conclude that applicants were not in possession of a reasonable number of macrophage-tropic- or T cell-tropic-specific inhibitory agents. The Examiner concluded that nothing in the disclosure points the

skilled artisan toward any particular class of agents, and accordingly, that the rejection is proper.

In response, applicants note that the Examiner repeats several grounds of rejection which applicants have already addressed hereinabove. However, in response to the Examiner's question regarding what structural and functional constraints govern the selection of any given agent, applicants reiterate that the nature of the agent is functionally constrained by the requirements that the agent (1) bind to a CD4+ cell susceptible to infection by a macrophage-tropic primary HIV-1 isolate, and (2) inhibit fusion of HeLa-env_{JR-FL} to a PM1 cell, but not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Applicants note that independent claims 7 and 20, as amended herein, clearly indicate that the agent inhibits the fusion of a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1 to the envelope of a macrophage-tropic primary isolate of HIV-1.

Applicants also again respectfully wish to correct the Examiner's misunderstanding that "[w]hile the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T cell-tropic isolates." In this regard, applicants again direct the Examiner's attention to the experimental data which show that each of PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see the specification at page 60, lines 13-16 and page 61, Table 3), but does <u>not</u> inhibit fusion of HeLa-env_{LAI} to a <u>HeLa-CD4+ cell</u> (see Table 3). Applicants note that the claimed invention recites the use of an agent which is not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Applicants contend that the Examiner appears to have overlooked the fact that it is not fusion of HeLa-env_{LAI} to <u>any</u> CD4+ cell that the agent must be incapable of inhibiting, but rather, it is fusion

to a HeLa-CD4+ cell. Applicants respectfully direct the Examiner's attention to page 61, Table 3 in the specification, which shows that PA-3, PA-5 and PA-7 inhibited fusion of HeLa-env_{LAI} to HeLa-CD4+ cells by 0%, and PA6 inhibited by a de minimis 7.7%. By comparison, PA-3, PA-5 and PA-6 inhibited fusion of HeLa-env_{JR-FL} to HeLa-CD4+ cells by 85, 96 and 92%, respectively, and PA7 inhibited by 67%. Thus, contrary to the Examiner's assertions, applicants maintain that the fusion-inhibitory activity of PA-3, PA-5, PA-6 and PA-7 meet the requirements of the pending claims. Applicants note that the HeLa-env_{JR-FL} and HeLa-env_{LAI} cell lines used in the RET assay reflect the fusion activity of macrophage-tropic and T cell-tropic HIV-1 strains, respectively (see the specification at, *inter alia*, page 52, lines 11-33 and pages 57-59).

Thus, in response to the Examiner's statement that "the disclosure fails to identify any suitable agents with the desired properties," applicants reiterate that the specification discloses the PA-3, PA-5, PA-6 and PA-7 monoclonal antibodies as examples of agents which meet the requirements of the agent recited in the claims. Applicants note that the β-chemokines, RANTES, MIP-1α and MIP-1β, may also qualify as examples of agents that satisfy the elements of the claims (see, *inter alia*, Table 4 in the specification).

In view of the remarks and arguments made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the "written description" ground of rejection set forth in the October 12, 2005 Office Action, and earnestly solicit allowance of all claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number

provided below.

A fee of SIXTY DOLLARS ($60.00) is required for a one-month extension of time for responding to the October 12, 2005 Office Action, and a check for this amount is enclosed. No other fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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